DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

March 6, 2000

Our Reference Number: 98-0137

Frederick T. Gates, Ph.D.
Genetics Institute, Inc.
One Burtt Road
Andover, MA 01810-5901

Dear Dr. Gates:

Your Biologics License Application for Antihemophilic Factor (Recombinant) [ReFacto®] for the control and prevention of hemorrhagic episodes and for short-term routine and surgical prophylaxis in patients with hemophilia A is approved effective this date. Genetics Institute, Inc. is hereby authorized to introduce or deliver for introduction into interstate commerce Antihemophilic Factor (Recombinant), manufactured under contract at the Pharmacia & Upjohn AB facility in Stockholm, Sweden under U.S. License No. 1163.

Under this license you are authorized to introduce or deliver for introduction into interstate commerce Antihemophilic Factor (Recombinant) in nominal dosage strengths of 250, 500 and 1000 IU per vial. Changes to the product, production process, location of production process, equipment, facilities, or responsible personnel are required to be reported to FDA as specified in Title 21 Code of Federal Regulations (CFR) Section 601.12.

The dating period for this product shall be 24 months from the date of manufacture when stored at 2-8° C. ReFacto® may also be stored at room temperature not to exceed 25 °C (77 °F) for up to 3 months. The date of manufacture shall be defined as the date of the initial sterile filtration of the formulated bulk. Results of ongoing stability studies should be submitted throughout the dating period as they become available.

We also acknowledge the following:

1. Your December 21, 1999 commitment to implement use of US licensed plasma in the manufacture of cell culture human serum albumin at the Pharmacia & Upjohn facility in Stockholm, Sweden ——— so that finished product will be available by ——— and ready for distribution by ———

2. Your February 7, 2000 commitment to submit updates on the ongoing validation studies for column resin life span by May 2000. We note your statement that the concurrent studies will include conductivity and TOC testing to evaluate the effectiveness of column regeneration.

3. Your February 7, 2000 commitment to introduce sterilizable spray bottles for [redacted] sanitization in environmentally classified areas.

4. Your February 24, 2000 commitment to revise the procedure for manual inspection of freeze-dried products (SOP 6017-05-OFI) to reduce the total acceptable defect level in ReFacto® from [redacted] In addition, we note that critical and non-critical defect limits will be reduced to reflect historical levels.

5. Your February 29, 2000 commitment to pre-clear educational material related to use of the one-stage and chromogenic assays.

6. Your March 2, 2000 commitment to monitor hemostatic efficacy in 25 surgical cases (10 cases already studied plus an additional 15 cases) using the chromogenic assay at the local lab to measure FVIII:C levels.

7. Your March 6, 2000 commitment to provide a detailed protocol for a randomized trial using two regimens for prophylaxis and submit a report to CBER containing the data and analyses on the feasibility of such a trial. If you elect not to undertake such a randomized controlled trial in routine prophylaxis, you will make your assessment available to the public including the power analysis based on your pharmacokinetic/pharmacodynamic model.

All adverse experience reports should be submitted according to 21 CFR 600.80 to the Center for Biologics Evaluation and Research (CBER), HFM-210, Food and Drug Administration, 1401 Rockville Pike, Rockville, Maryland 20852-1448. In addition, safety related information obtained in the course of the ongoing clinical studies should be reported to BB-IND 5348 in accordance with 21 CFR 312.32. It is also requested that distribution reports be submitted according to 21 CFR 600.81.

Antihemophilic Factor (Recombinant) manufactured by Genetics Institute, Inc. is exempt from the lot release requirements of 21 CFR 610.2. However, we acknowledge your agreement to submit samples and release protocols, for one year, for each lot of Antihemophilic Factor (Recombinant) released for distribution in the United States. In subsequent years you will submit samples and release protocols for each nominal dosage strength from one lot per year.

Please submit three (3) copies of final printed labeling at the time of use accompanied by Part II of FDA 2567 with completed implementation information. In addition, you may wish to submit your proposed introductory advertising and promotional campaign. If so, please submit three (3) copies of the proposed material in draft form with Part I of the FDA Form 2567/2253 to CBER, Advertising and Promotional Labeling Staff (APLS), HFM-602, 1401 Rockville Pike, Rockville,

Maryland 20852-1448. Promotional claims should be consistent with and not contrary to the approved labeling. No comparative claims or claims of superiority over other similar products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research. Final copies of advertising and promotional materials should be submitted at the time of use with Part II of FDA Form 2567/2253 to APLS. Please include copies of the approved labeling with your proposed or final copy of advertising and promotional materials submitted to CBER.

Sincerely yours,

Jay S. Epstein, M.D.
Director
Office of Blood Research and Review
Center for Biologics
Evaluation and Research